

Active processes make lipid membranes either flat or crumpled

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Abstract

Motivated by the long-standing open questions on miscibility phase transitions (MPTs) in live cell membranes, we construct a hydrodynamic theory for lipid membranes embedded in an active medium. We use this to make several testable predictions: (i) generic *active stiffening* with orientational long range order (flat membrane) or *softening* with crumpling of the membrane, controlled by the *active tension* and (ii) for mixed lipid membranes, capturing the nature of putative MPTs by measuring the membrane conformation fluctuations. Possibilities of both first and second order MPTs in mixed membranes are argued for. Near second order MPTs, active stiffening manifests as novel positional *nearly long range order*.

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Cell membranes, made of several lipids [1], are affected by cell biological active (nonequilibrium) processes (e.g., membrane pumps [2] and the nonequilibrium fluctuations of the cell cytoskeleton, an *active fluid*) [3]. Occurrence of miscibility phase transitions (MPTs) in eukaryotic cell plasma membranes, well-studied in *equilibrium* heterogeneous or mixed model lipid bilayers and giant plasma membrane vesicles (GPMVs) [4, 5], remains controversial till date [6]. Whether cellular active processes can control membrane fluctuations and associated MPTs in mixed membranes and if so, how, form the general motivations for the present study.

In this Letter, we construct a hydrodynamic theory for planar lipid (fluid) membranes [1] in active fluids and study the membrane conformation fluctuations and the associated active MPTs. We assume an active fluid with orientable degrees of freedom [3] in its isotropic phase, i.e., without any orientational long range order (LRO) [7]. Our predictions are quite general and testable in mixed model lipid bilayers and GPMVs in an isotropic actomyosin extract with adenosine triphosphate (ATP), or in an isotropic solution of live orientable bacteria [8].

In order to focus on the essential physics of the problem, we consider a two-component, inversion-symmetric [9], single-layered lipid membrane [10] with surface tension σ and bending modulus κ , immersed in an isotropic *active fluid* [3]. In stark contrast to equilibrium lipid membranes [11, 12], our model displays generic stiffening and statistical flatness (softening and crumpling) of the membrane at all temperatures T , due to positive (negative) active tension σ_a , or equivalently, positive (negative) active corrections to κ , which diverge in the hydrodynamic limit. We speculate the existence of both nonequilibrium second order MPTs (SMPT) through critical (CP) and tricritical (TP) points, and first order MPTs (FMPT) in the model, unlike only SMPT in the equilibrium limit that belongs to the two-dimensional (2d) Ising universality class [5]. Describing the planar membrane conformations in terms of a single-valued height field $h(\mathbf{x}, t)$ and local normal $\mathbf{n} = (-\nabla h, 1)$ at the membrane in the Monge gauge [13], at 2d for positive σ_a , this implies

$$\Delta_n = \langle (\delta \mathbf{n}(\mathbf{x}, t))^2 \rangle = \text{const.}, \Delta_h = \langle h(\mathbf{x}, t)^2 \rangle = \tilde{A} \ln L, \quad (1)$$

in the thermodynamic limit (TL), implying orientational LRO, hence statistical flatness and positional quasi long range order (QLRO), \tilde{A} is a *nonuniversal amplitude*. Near CP, the

membrane becomes *super stiff*:

$$\Delta_h = \tilde{G} \ln \ln L, \quad (2)$$

in TL, an L -dependence weaker than the $\ln L$ -dependence in QLRO, which we call *nearly long range order* (NLO), not observed in equilibrium fluid membranes. Here, \tilde{G} is another nonuniversal amplitude, and $\delta \mathbf{n} = -\nabla \mathbf{h}$ is the deviation of \mathbf{n} . In contrast, for sufficiently large negative σ_a in $2d$, Δ_n and Δ_h diverge for membranes larger than a *persistence length* ζ [12], indicating only orientational and positional short range orders (SRO).

For an incompressible mixed membrane composed of two lipids, say A and B, of concentrations n_A and n_B , respectively [12], $n_A + n_B = 1$. The local inhomogeneity $\phi (= n_A - n_B)$ is the order parameter for the MPT; $\phi = 0$ identically for a pure membrane. The local orientation field of the embedding isotropic active medium is described by a director field \mathbf{p} [14], whose fluctuations relax *fast* [7, 15] and are not hydrodynamic variables. Since the active processes may in general interact differently with A and B, we relax the usual inversion symmetry of ϕ for a binary mixture [16] when coupled to local mean curvatures in the present model (see Refs. [12, 17] in this context). Then, symmetry considerations (e.g., translation, in-plane rotation, inversion symmetry of h and invariance under tilt for the membrane) enforce the general forms of the dynamical equations for h (a nonconserved variable) and ϕ (a conserved density, since n_A, n_B are conserved) to the lowest order in gradient expansions, as

$$\begin{aligned} \frac{\partial h}{\partial t} = & \Gamma_h [-\kappa \nabla^4 h + (\lambda \phi^2 + \tilde{\lambda} \phi) \nabla^2 h + (\sigma + \alpha) \nabla^2 h] \\ & + f_h, \end{aligned} \quad (3)$$

$$\begin{aligned} \frac{\partial \phi}{\partial t} = & \Gamma_\phi \nabla^2 [r \phi - \nabla^2 \phi + \frac{u}{3!} \phi^3 + 2\lambda_1 \phi (\nabla^2 h)^2 \\ & + 2\lambda_2 (\nabla^2 h)^2 + v \phi^5] + \nabla \cdot \mathbf{f}_\phi. \end{aligned} \quad (4)$$

In (3), λ , $\tilde{\lambda}$ and α , coefficients of the nonequilibrium terms that generate σ_a (see Supplemental Material (SL) below), can be positive or negative. The active terms with coefficients $\lambda, \tilde{\lambda}$ are forbidden in equilibrium due to the tilt invariance of the associated free energy [12]. They are, however, permitted here as the tilt invariance in the present problem must hold at the level of the equations of motion. Remaining terms in (3) and (4) can be obtained from a free energy functional \mathcal{F} ; see SL. Parameter $r = T - T_c$, T_c being the equilibrium mean field critical temperature of the MPT [18] without height fluctuations; couplings $u, v > 0$.

The form of (4) yields SMPT belonging to the 2d Ising universality class in the equilibrium limit ($\lambda = 0 = \tilde{\lambda}$) [5]. Γ_ϕ (a constant) and Γ_h are kinetic coefficients. For frictional and Stokesian ambient fluid flows, Γ_h is a constant and $1/(4\eta q)$, respectively, where q is a wavevector and η is the ambient fluid viscosity [19]. Noises f_h and \mathbf{f}_ϕ are zero-mean, Gaussian distributed with variances in the Fourier space **given by** $\langle f_h(\mathbf{q}, \omega) f_h(\mathbf{q}', \omega') \rangle = 2D_h \Gamma_h \delta(\mathbf{q} + \mathbf{q}') \delta(\omega + \omega')$, $\langle f_{\phi i}(\mathbf{q}, \omega) f_{\phi j}(\mathbf{q}', \omega') \rangle = 2D_\phi \Gamma_\phi \delta_{ij} \delta(\mathbf{q} + \mathbf{q}') \delta(\omega + \omega')$; $D_h \neq D_\phi$ in general.

To motivate the terms with coefficients $\lambda, \tilde{\lambda}, \alpha$ in (3), consider an inversion-symmetric, mixed, planar fluid membrane placed in an active suspension of actin filaments [3] in its isotropic phase. Now assume that the filaments are grafted normally on the membrane such that $\mathbf{p} \cdot \mathbf{n} = 1$. This yields $p_j = \partial_j h$ ($j = x, y$) to the linear order in height fluctuations [20]. The general form of $v_z(z = h)$, the z -component of the local normal ambient active fluid velocity at the lipid membrane is of the general form $v_z/\Gamma_h = \delta\mathcal{F}/\delta h + X(\phi)\partial_j p_j = \delta F/\delta h + X\nabla^2 h$ to the linear order in ∇h , consistent with the inversion-symmetry (ignoring geometric nonlinearities; see SL). The physical content of the above form of v_z is that a local splay of \mathbf{p} at $z = h$ can create an active force that may reinforce or weaken the corresponding equilibrium contribution $\delta\mathcal{F}/\delta h$ [19]. Now, with the choice $X(\phi) = \lambda\phi^2 + \tilde{\lambda}\phi + \alpha$, together with the kinematic boundary condition for an impermeable membrane, i.e., $\partial h/\partial t = v_z$, we recover (3). Now imagine regions of nonzero mean curvature with excess lipid of one kind so that ϕ picks up a non-zero value with a specific sign. Such a region then either pulls up the curved region further (instability) or tries to flatten the curvature (stable membrane) due to the active processes; see Fig. 1 for a schematic picture. Coupling $\tilde{\lambda}$ determines the asymmetric dependence of v_z on A or B. For an active fluid with actin filaments and motors, $\lambda, \tilde{\lambda}, \alpha$ should scale with the concentration C_0 of the ATP molecules and the free energy released due to the hydrolysis of ATP, $\Delta\mu \sim 10^7 kCal/(500 \times 10^{23})$ [21].

The lack of experimental and theoretical knowledge about the order of MPTs in a symmetric mixed membrane embedded in an active fluid demands that we must allow for the possibility of both FMPT and SMPT, and study their connections with the membrane fluctuations separately. We present theoretical arguments in favor of both FMPTs and SMPTs later in the text. For a pure lipid membrane, positive (negative) α will increase (decrease) its effective surface tension $\sigma' = \sigma + \alpha$. Thus, depending on its magnitude and sign, α can lead to either stiffening or softening including crumpling of the pure membrane. In order

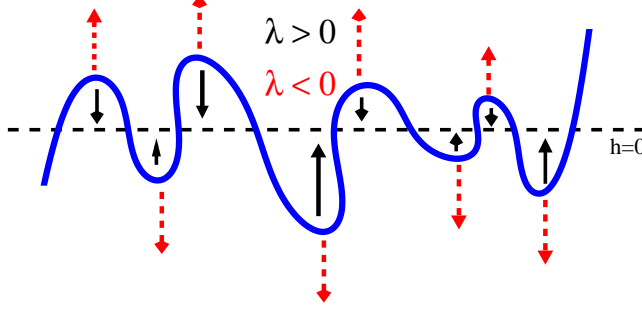


FIG. 1: (Color online) Schematic representations of the active forces ($\tilde{\lambda} = 0$) on the membrane (blue curved line) for $\lambda > 0$ (stabilizing, solid black arrows) and $\lambda < 0$ (destabilizing, broken red arrows). A non-zero $\tilde{\lambda}$ leads to further ϕ -dependent modification of the active force (not shown)

to highlight the role of heterogeneity on the nonequilibrium dynamics of mixed membranes, we set $\sigma' = 0$; see SL. From (3), we extract a q -dependent *effective bending modulus*, $\kappa_e(q)$ or an *active tension* σ_a for any $\lambda \neq 0$

$$\kappa_e = \kappa + \frac{\lambda}{q^2} \langle \phi^2 \rangle, \quad \sigma_a = \lambda \langle \phi^2 \rangle, \quad (5)$$

at all T (see SL); σ_a is positive (negative) for $\lambda > (<)0$. This suggests generic stiffening (softening) of the membrane for $\lambda > (<)0$ at *any* T , in contrast to an isolated fluid membrane in equilibrium [12]. Now assume $\lambda > 0$. Since $\langle \phi^2 \rangle$ is larger in the ordered phase as $\langle \phi \rangle = m \neq 0$, $\Delta\kappa(q) = \kappa_e(q) - \kappa$ is larger in the ordered phase. With (5) and $\lambda > 0$, Δ_n is finite in TL (i.e., orientational LRO), independent of the nature of MPTs. Now for a putative FMPT at $T = T^*$, we write $\kappa_e(q) = \kappa + \lambda \langle \phi^2 \rangle / q^2$ ($T > T^*$), and $\kappa_e(q) = \kappa + \lambda m^2 / q^2$ ($T < T^*$), ignoring ϕ -fluctuations in comparison with m^2 . Thus, there is a *jump* in κ_e , that is large for small q , as T crosses T^* . Furthermore, $\Delta_h = \tilde{A} \ln L$, implying positional QLRO; see Eq. (1). Both Δ_n , Δ_h are *discontinuous* across T^* , due to the discontinuity in $\kappa_e(q)$ across FMPT. In contrast, for SMPT $\langle \phi^2 \rangle$ is continuous across $T = T_c$ and rises as $r(T)$ approaches 0; also $m = 0$ for $T \sim T_c$. Thus $\kappa_e(q)$, as given by (5), rises smoothly as T_c is approached from either side; see Fig. 2. This yields $\Delta_h = \tilde{G} \ln L$ in TL, implying positional QLRO for both $T > T_c$, $T < T_c$; giving Eq. (1) above; $\tilde{G} = \frac{D_h}{\lambda D_\phi}$. Unlike FMPT, both Δ_n and Δ_h are continuous across T_c for SMPT. In contrast, in the equilibrium limit Δ_n scales as $\ln \ln L$ at $T = T_c$ [12], thus exhibiting NLO only; at all other T , the membrane is crumpled at large scales. There is no FMPT in [12]. Variations of $\kappa_e(q)$ around FMPT and SMPT for a given q are shown schematically in Fig. 2; see Table I summarizing our results

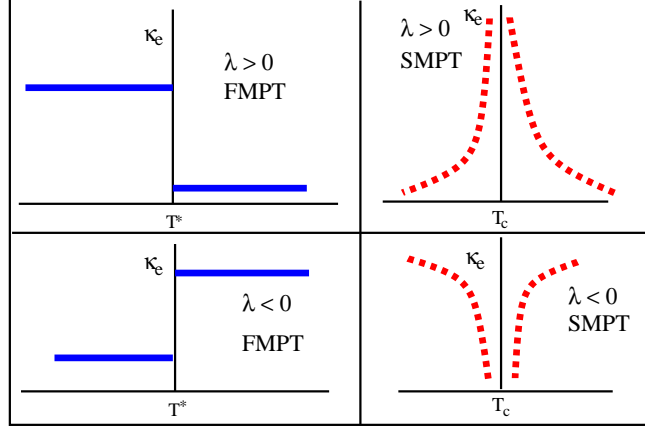


FIG. 2: (Color online) Schematic variation of $\kappa_e(q)$ across FMPT (left) and SMPT (right) for both $\lambda > 0$ (top) and $\lambda < 0$ (bottom). Smooth (discontinuous) variations of κ_e across T_c (T^*) are shown (see text).

on $\kappa_e(q)$, Δ_n , Δ_h across MPTs.

Large ϕ -fluctuations very close to CP should qualitatively change $\kappa_e(q)$. For simplicity, we set $\tilde{\lambda} = 0 = \lambda_2$, such that the Ising symmetry for ϕ is restored. This suffices for our purposes here, since we are interested in SMPT only. We find a *renormalized*

$$\kappa_e(q) = \kappa + \frac{\lambda D_\phi}{q^2} \int_q \frac{d^2 q_1}{(2\pi)^2} \frac{1}{r + q_1^2} \approx -\frac{G}{q^2} \ln q, \quad (6)$$

for small q near CP ($r \approx 0$); $G = \lambda D_\phi$; see SL for some calculational details. Then $\Delta_n = -\frac{D_h}{G} \int \frac{q dq}{\ln q} \sim \text{const.}$ in TL and $\Delta_h = (D_h/G) \ln \ln L$, establishing orientational LRO and positional NLO with D_h/G as the nonuniversal amplitude; see Eq. (2). Notice that, in general Δ_n remains finite at all $T \neq T_c$ and even across FMPT. Nonetheless, at T_c , Δ_n is further suppressed in comparison to its values elsewhere in the phase space. This result holds with or without the ambient fluid hydrodynamics. Thus, active stiffening considerably enhances as CP is approached, yielding a *super-stiff* membrane at CP. A schematic phase diagram in the $\lambda - T$ plane is shown in Fig. 3; see SL.

For $\lambda < 0$, $\kappa_e(q) < 0$ for sufficiently low q , implying long wavelength instability for the planar membrane or *membrane crumpling*. In general, larger $\langle \phi^2 \rangle$ in the ordered phase leads to a smaller $\kappa_e(q)$. We define a persistence length ζ , such that for $q = 2\pi/\zeta$, $\kappa_e(\zeta) = 0$ [12, 23]. Physically, for length scales $L < \zeta$ the membrane appears flat on average, where as for $L > \zeta$, it is crumpled. Due to the strong dependence of κ_e on the nature of the transition (FMPT or SMPT), ζ also depends strongly on it. In particular, across an FMPT

at T^* , $\zeta = \frac{\sqrt{\kappa/|\lambda|}}{\sqrt{\langle\phi^2\rangle}}$, for $T > T^*$ and $\zeta = \frac{\sqrt{\kappa/|\lambda|}}{m}$ for $T < T^*$, showing a jump in ζ . In contrast, there is no discontinuity in ζ at SMPT at $T = T_c$: ζ satisfies the equation: $\zeta^2 \ln \zeta = \frac{\kappa}{D_\phi \lambda}$ at T_c . Both Δ_n and Δ_h diverge at finite $L \sim \zeta$, demonstrating only orientational and positional short range order. Due to the large fluctuations of ϕ at CP, $\zeta(CP) \ll \zeta(T \neq T_c)$, giving *super-crumpling* of the membrane, in contrast to super stiffness for $\lambda > 0$ at CP [22]; see Table I. Considering λ as a tuning parameter, the change in the membrane fluctuations with

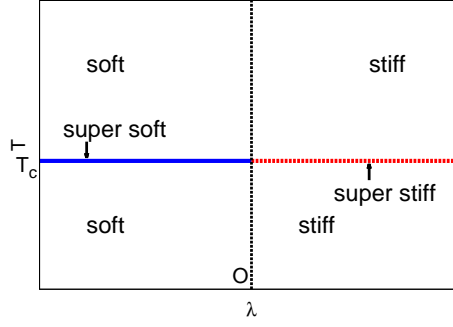


FIG. 3: (Color online) Schematic phase diagram in the $\lambda - T$ plane ($\tilde{\lambda} = 0$). Super-stiff and super-crumpling lines are marked. The solid horizontal (blue) and broken vertical lines refer to $T = T_c$ and $\lambda = 0$, respectively.

λ , represented by Δ_n at a fixed T may be viewed as a *structural phase transition* at $\lambda = 0$, such that for $\lambda > (<)0$, ζ becomes infinite (finite). An order parameter for this transition may be constructed as in [12, 23].

We now heuristically analyze the MPTs. At the mean-field (MF) level consider constant order parameter $\langle\phi\rangle = m$ and negative of the mean curvature $\langle\nabla^2 h\rangle = C = 0$ (due to the inversion symmetry of h). Then m follows the same Landau MF equation in the steady state as for the equilibrium Ising model [24], confirming only SMPT at MF level. To proceed beyond MF, in the spirit of low-order perturbation theories, we decouple the nonlinear terms which couple the dynamics of h and ϕ (see SL). This yields a modified free energy F' , parametrized by u_e (fluctuation-corrected u) calculated perturbatively in $\tilde{\lambda}, \lambda_2$, that now determines the phases of ϕ , in analogy with equilibrium Landau MF theories.

With $\lambda > 0$ the inhomogeneous *active* one-loop correction to u that may be tuned to change the sign of u_e is (this suffices for our arguments here) $\Delta u = \frac{18\lambda_2\tilde{\lambda}^3}{3!} \int^\Lambda \frac{d^2q}{(2\pi)^2} \frac{d\Omega}{2\pi} (-q^6) C_{hh}(q, \Omega) G_h(q, \Omega)^3$, such that $u_e = u + \Delta u$, where Ω is a frequency and

$G_h(q, \Omega)(= \langle \delta h / \delta f_h \rangle)$ is the propagator of $h(\mathbf{q}, \Omega)$ and $C_{hh} = \langle |h(\mathbf{q}, \Omega)|^2 \rangle$ is the height-height correlator. Λ is an upper wavevector cut off; see SL for some details. In particular, with the forms for G_h and C_{hh} in SL, we obtain $\Delta u = \lambda_2 \tilde{\lambda}^3 D_h A$, where, A is a numerical constant. Thus, for $u_e = u + \lambda_p \tilde{\lambda}^2 D_h A > (<)0$, $\lambda_p = \tilde{\lambda} \lambda_2$, SMPT (FMPT) ensues, in analogy with the known equilibrium MF results [24]. Then, $u_e < 0$ yields an FMPT transition temperature $T^* = T_c + 2u_e^2/(3v)$ and $m^2 = |u_e|/(2v)$ analogous to corresponding equilibrium results [24]. For $u_e > 0$, usual SMPT follows at $r = 0$, ignoring any fluctuation correction to r . At TP, $u_e = 0$, i.e., $u = -\lambda_2 \tilde{\lambda}^3 D_h A$. Notice that unlike equilibrium examples of TP [24], here the condition for TP explicitly involves D_h , thus bearing the hallmark of nonequilibrium [25]. Fluctuation induced shifts in T_c and T^* due to $\lambda_p \neq 0$ is argued to be of the same order as in equilibrium 2d Ising model due to u (see SL), suggesting T_c, T^* to be experimentally accessible for inversion-symmetric mixed membranes. We are, thus, led to conclude that inversion-symmetric lipid membranes should undergo MPTs within experimentally accessible temperature ranges. A schematic phase diagram of the model in the $u - \lambda_p$ plane with $\lambda > 0$ is shown in Fig. 4.

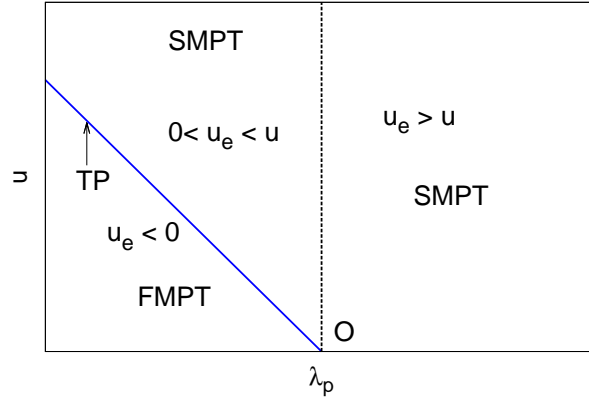


FIG. 4: (Color online) Schematic phase diagram in the $u - \lambda_p$ plane ($\lambda > 0$). Inclined blue line marks the line of TP (boundary between FMPT and SMPT). Symbol O marks the origin $(0, 0)$.

We have thus developed a hydrodynamic theory for inversion-symmetric membranes embedded in isotropic active fluids. Our results can be directly tested in *in-vitro* experiments on GPMVs or model lipid bilayers immersed in an isotropic active suspension of actin filaments. We establish that the interplay between heterogeneity and the active processes leads to the nontrivial fluctuation properties of the mixed membranes, distinguishing them from

their pure counterparts. Since measuring h -fluctuations, e.g., by spectroscopic methods [27], yields κ_e , we clearly provide a way to ascertain the sign of λ and the nature of MPT *without* measuring ϕ -fluctuations. For a jump in κ_e at a given $T = T^*$, it must be FMPT; else, if $\kappa_e(q)$ rises smoothly and diverges at some $T = T_c$ as $q \rightarrow 0$, the system displays SMPT. Furthermore, if $\kappa_e|_{disorder} < (>) \kappa_e|_{order}$, then $\lambda > (<) 0$. ATP depletion methods [26] can be used to control the magnitude of λ and $\tilde{\lambda}$; the sign of λ may be tuned by using contractile or extensile active fluids [3]. The sign of λ_p , crucial in our theory for fixing the order of MPT, may be varied by using different sets of lipids. We expect our theory to introduce new directions in the physical understanding of living cell membrane dynamics with new vistas of striking nonequilibrium phenomena. We look forward to experimental tests of our predictions on GPMVs and live cell membranes.

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λ	Stiff/soft	FMPT at $T = T^*$	SMPT at $T = T_c$
$\lambda > 0$	Generic stiff at all T	Jumps in $\kappa_e(q), \Delta_n$ finite \Rightarrow orientational LRO, $\Delta_h \sim \ln L \Rightarrow$ positional QLRO	$\kappa_e(q)$ rises smoothly as $T \rightarrow T_c$, Δ_n smooth, finite at all $T \Rightarrow$ orientational LRO, $\Delta_h \sim \ln L$ (smooth, QLRO) for $T \neq T_c$ and $\sim \ln \ln L$ (NLO) as $T \approx T_c$
$\lambda < 0$	Generic soft/ crumpling at all T	Finite ζ , $\zeta(T > T^*) > \zeta(T < T^*)$	Finite ζ , $\zeta(T_c) \ll \zeta(T \neq T_c)$

TABLE I: Variation of $\kappa_e(q), \Delta_n, \Delta_h$ at different T for positive and negative λ .

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I. SUPPLEMENTAL MATERIAL

A. Free energy functional for a mixed fluid membrane in equilibrium

In the absence of the active terms ($\lambda = 0 = \tilde{\lambda}$), Eqs. (3) and (4) can be obtained from a free energy functional \mathcal{F} , taking into account the relevant symmetries mentioned above:

$$\begin{aligned} \mathcal{F} = \int d^d x & \left[\frac{\sigma}{2} (\nabla h)^2 + \frac{\kappa}{2} (\nabla^2 h)^2 + \lambda_1 \phi^2 (\nabla^2 h)^2 \right. \\ & \left. + \lambda_2 \phi (\nabla^2 h)^2 + \frac{r}{2} \phi^2 + \frac{1}{2} (\nabla \phi)^2 + \frac{u}{4!} \phi^4 + \frac{v}{6} \phi^6 \right]. \end{aligned} \quad (7)$$

Equation (4) may be written as

$$\frac{\partial \phi}{\partial t} = \Gamma_\phi \nabla^2 \frac{\delta \mathcal{F}}{\delta \phi} + \nabla \cdot \mathbf{f}_\phi. \quad (8)$$

For a pure membrane ($\phi = 0$), (3) can be obtained from an effective free energy by replacing σ by $\sigma' = \sigma + \alpha$ in \mathcal{F} :

$$\frac{\partial h}{\partial t} = -\Gamma_h \frac{\delta F_h}{\delta h} + f_h, \quad (9)$$

where $F_h = \int d^2x [\sigma'(\nabla h)^2/2 + \kappa(\nabla^2 h)^2/2]$, $\sigma' = \sigma + \alpha$. Thus, for a pure membrane, the active effects may be wholly described by a modified equilibrium free energy F_h . For a mixed membrane, there is no such general equivalence with a simply modified equilibrium model.

Equation (4) does not contain any *active* ϕ^2 -term in its rhs. Such a term would survive even for $h = \text{const.}$, where as active processes here are assumed to couple with the membrane via mean curvature $\nabla^2 h$, and hence all active effects on the membrane should vanish for $h = \text{const.}$. This rules out an active pure ϕ^2 term in (4).

In (3) and (4), we have neglected the geometric nonlinearities, which are irrelevant (in a scaling sense) near SMPTs. These originate from the nonlinear forms of the area element and mean curvature [13]. These are irrelevant near CP in a scaling sense. Across FMPT these may affect the first order transition temperature T^* (see main text) and order parameter m quantitatively; however, our general conclusions are expected to remain unchanged.

Notice that \mathcal{F} above with $\sigma = 0$ is identical to that in Ref. [12]. As in Ref. [12], \mathcal{F} allows for an SMPT. At CP, couplings λ_1, λ_2 are *irrelevant* in a scaling sense, ensuring 2d Ising universality class for the order parameter in the equilibrium limit.

B. Effective bending modulus

In general, from (3)

$$\kappa_e(q) = \kappa + \frac{\lambda}{q^2} \langle \phi^2 \rangle + \frac{\tilde{\lambda}}{q^2} \langle \phi \rangle, \quad \sigma_a = \lambda \langle \phi^2 \rangle + \tilde{\lambda} \langle \phi \rangle. \quad (10)$$

Since ϕ is a conserved density, $\langle \phi \rangle = 0$ when averaged over the whole system (assuming there is no excess of A or B lipids). In case of macroscopic domains in the ordered phase, if κ_e or σ_a is defined over a single of domain, either A or B rich, it will depend explicitly on the domain type. Specifically, depending upon the sign of $\tilde{\lambda}$, κ_e or σ_a should be larger in either A- or B-rich domains. For sufficiently large $|\tilde{\lambda}|$ with $\tilde{\lambda} \langle \phi \rangle < 0$ in a given domain,

$$\kappa_e = \kappa + \frac{\lambda}{q^2} \langle \phi^2 \rangle - \left| \frac{\tilde{\lambda}}{q^2} \langle \phi \rangle \right|, \quad \sigma_a = \lambda \langle \phi^2 \rangle - |\tilde{\lambda} \langle \phi \rangle|. \quad (11)$$

For SMTP, near T_c , $\langle\phi\rangle \approx 0$, and hence, the term with coefficient λ automatically dominates. Thus, the sign of σ_a is necessarily controlled by λ and our results near T_c as elucidated in the main text apply. Away from and below T_c or below T^* (for SMPT), it is possible that the term with coefficient $\tilde{\lambda}$ in the above equation dominates and κ_e or σ_a can be negative in that domain. Thus, it is possible to introduce crumpling instability in that domain, where as κ_e remains positive in the other domain (and diverges for $q \rightarrow 0$) and hence, the other domain should be statistically flat. This is testable in experiments. The term with coefficient $\tilde{\lambda}$ has no effect on κ_e in the disordered phase ($\langle\phi\rangle = 0$), independent of FMPT or SMPT.

C. Analysis of MPTs

At the lowest order perturbation theories, the cross coupling terms in (3) and (4) may be decoupled to arrive at (in the Fourier space)

$$\partial_t h = -\Gamma_h \kappa_e(q) q^4 h + f_h, \quad (12)$$

and

$$\partial_t \phi = -\Gamma_\phi q^2 \frac{\delta F_\phi}{\delta \phi} + i \mathbf{q} \cdot \mathbf{f}_\phi, \quad (13)$$

at the lowest order. Here, $\kappa_e(q)$ is the fluctuation-corrected bending modulus as given in (6); F_ϕ is an effective fluctuation-corrected free energy functional of the order parameter ϕ . When written in terms of the fluctuation-corrected parameters (in the real space):

$$F_\phi = \int d^d x \left[\frac{r}{2} \phi^2 + \frac{1}{2} (\nabla \phi)^2 + u_e \phi^4 + \frac{v}{6} \phi^6 \right]. \quad (14)$$

At this level of lowest order decoupling, thus, the dynamics of ϕ is now effectively decoupled from h and the phases of ϕ may now be determined from F_ϕ , that controls the dynamics of ϕ at this level of approximation. Here, u_e is the fluctuation-corrected u (see Sec. I D for more details). While in general all the parameters in \mathcal{F} should receive fluctuation corrections from $\tilde{\lambda}, \lambda_2$, we only concern ourselves with the corrections to u . This suffices for our purposes here.

D. Active inhomogeneous fluctuation correction to u

The lowest order active inhomogeneous fluctuation correction to u may be represented by the following Feynman diagram.

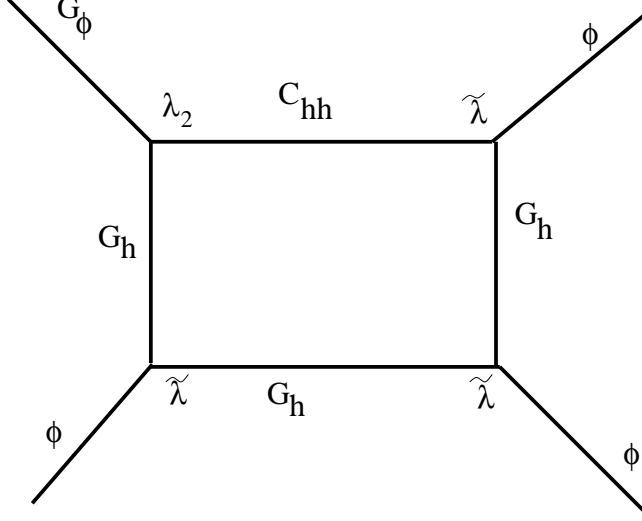


FIG. 5: Active fluctuation correction to effective u due to $\tilde{\lambda}, \lambda_2$.

The bare correlator function for h is given by $C_{hh}(q, \Omega) = \langle |h(q, \Omega)|^2 \rangle = \frac{2D_h}{\Omega^2 + \Gamma_h^2 \kappa^2 q^8}$. $G_\phi(q, \Omega) = \frac{1}{-i\Omega + \Gamma_\phi q^2(r+q^2)}$ and $G_h(q, \Omega) = \frac{1}{-i\Omega + \Gamma_h \kappa q^4}$ are the bare propagators for ϕ and h , respectively.

E. DRG flow equations and fixed points

Large critical point fluctuations very close to SMPT may be systematically handled within dynamic renormalization group (DRG) frameworks [28, 29]. With $\tilde{\lambda} = 0 = \lambda_2$, simple power counting shows that the nonlinear coefficients λ and u are *equally relevant* (in a scaling/DRG sense) at 2d, the physically relevant dimension, with both being *marginal* at $d = 4$. This calls for a perturbative DRG calculation together with an ϵ -expansion, $\epsilon = 4 - d$ [28, 29]. In this limit, the model admits only SMPT belonging to the 2d Ising universality class. The one-loop DRG procedure formally involves the following steps (i) obtaining the fluctuation corrections to the different model parameters by integrating out the high wavevector parts of the fields from Λ/b to Λ , $b > 1$, (ii) rescaling the fields wavevector \mathbf{q} , frequency ω by $\mathbf{q}' = b\mathbf{q}$, $\omega' = b^z\omega$ and rescaling of the fields h and ϕ accordingly [28]. With $b = e^l \approx 1 + l$, $l \ll 1$, the resulting DRG recursion relations for the coupling constants u and λ yield

$$\frac{du}{dl} = u[\epsilon - 9uD_\phi], \quad (15)$$

$$\frac{d\lambda}{dl} = \lambda[\epsilon - 3uD_\phi - 4\tilde{\Gamma}\lambda D_\phi], \quad (16)$$

where $\tilde{\Gamma} = \frac{\Gamma_h}{\Gamma_\phi + \kappa\Gamma_h}$. For the flow equations (15) and (16), stable fixed point (FP) $u^* = \frac{\epsilon}{9D_\phi}$; in addition, if ambient fluid hydrodynamics is considered, then $\lambda^* = \frac{\kappa\epsilon}{6D_\phi}$. Else, for a fixed background or for a frictional flow of the ambient fluid $\lambda^* = \frac{\epsilon}{6\tilde{\Gamma}D_\phi}$. Not surprisingly, u^* yields the critical exponents at SMPT identical to their values at the Heisenberg FP of the Ising model in equilibrium, consistent with the expectation that the SMPT belongs to the Ising universality class. At the one-loop order, there are no fluctuation corrections to $\Gamma_h, \Gamma_\phi, D_h$ and D_ϕ . Then, in a perturbative DRG calculation expanding in terms of the relevant (in a scaling/DRG sense) couplings u and λ , renormalized

$$\kappa_e(q) = \kappa + \frac{\lambda D_\phi}{q^2} \int_{\Lambda/b}^{\Lambda} dq_1 \frac{q_1^{d-1}}{r + q_1^2} \approx -\frac{G^*}{q^2} \ln q, \quad (17)$$

at $d = 2$ for small q at the DRG FP or CP. Here, at the DRG fixed point $G^* = \lambda^* D_\phi = \epsilon/(6\tilde{\Gamma})$ without ambient fluid hydrodynamics (and $G^* = \kappa\epsilon/6$ for Stokesian fluid for small q). Constant Λ is an upper wave-number cut-off. Then $\Delta_n = \frac{D_h}{G^*} \int \frac{q dq}{\ln q} \sim \text{const.}$ and $\Delta_h = \frac{D_h}{G^*} \ln \ln L$ in TL. Clearly, the amplitude D_h/G^* is nonuniversal and these results are in agreement with results obtained in the main text; the amplitudes continue to be nonuniversal at the DRG FP. Lastly, the lack of renormalization of Γ_h and Γ_ϕ at the one-loop order implies that dynamic exponent $z = 4$ at SMPT for both h and ϕ , respectively (strong dynamic scaling), without ambient flows and $z = 3$ and $z = 4$ for h and ϕ , respectively (weak dynamic scaling), when ambient flows are considered [29].

In the above, although we have neglected λ_2 and $\tilde{\lambda}$, the effective coupling $\lambda_p = \tilde{\lambda}\lambda_2$ becomes marginal at $D = 4$, and hence should be *equally relevant* as u and λ in a DRG sense. Indeed, there are additional one-loop corrections to the various bare model parameters that originate from λ_p (not shown here). Thus, the resulting SMPT is not expected to belong to the Ising universality class. Still, in the spirit of the ϵ -expansion, $\kappa_e(q)$ should scale as $\frac{-\ln q}{q^2}$ to the leading order in ϵ at the stable DRG FP. Thus, our results of a finite Δ_n and Δ_h going as $\ln \ln L$ for large L and hence orientational LRO and positional NLRO should survive.

F. Fluctuation induced shift in T_c

Nonzero λ_p should lead to a fluctuation-induced shift in T_c . The corresponding Feynman diagram is shown in Fig. 6. The expression is of the form $\sim \lambda_p D_h \int \frac{d^2 q}{(2\pi)^2 \kappa^2 q^2}$.

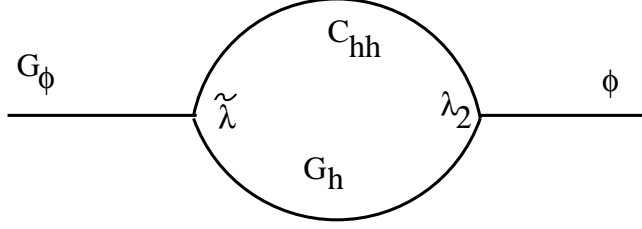


FIG. 6: Correction to T_c coming from λ_p . Clearly, the contribution being log-divergent only produces only produces a shift comparable to the fluctuation-induced shift of T_c in equilibrium coming from the $u\phi^3$ -term in Eq. (4).

Simple power counting argument yields that the one-loop diagram corresponding to this shift has the same divergence as the one-loop diagram giving the shift in T_c in equilibrium Ising model. This suggests that this additional shift of nonequilibrium origin has a similar magnitude as that for equilibrium Ising model. Hence, renormalized T_{cR} , the shifted or fluctuation-corrected T_c , and correspondingly, any putative SMPT should be accessible in experiments. Furthermore, if we construct an effective Landau MF in terms of u_e and T_{cR} , the first order transition temperature T^* also gets a shift. Since T_{cR} is expected to be experimentally accessible, the shifted T^* should also be accessible experimentally. Thus, we conclude that inversion-symmetric lipid membranes should undergo MPTs (FMPT or SMPT) within experimentally accessible temperature ranges. The above analysis has been done in the spirit of bare perturbation theories, in terms of the bare model parameters. We note that if we use κ_e instead of κ , the above diagram would not have given any diverging contribution to T_c and only the equilibrium correction would be relevant. Thus our conclusion that shifted T_c and T^* are within experimentally accessible temperature ranges remains valid.